

17. REPRODUCTIVE TOXICITY

Test substance:

Thiodiethylene bis (3,5-di-tert-butyl-4-hydroxyhydro
cinnamate)
CAS No. 41484-35-9

The requirement for reproductive toxicity testing is met by the availability of 90-day repeat dose testing with appropriate analysis of reproductive organs and a developmental toxicity test. This summary describes the available repeat dose testing. The developmental study will be conducted following EPA review of this submission.

Three repeat dose studies are available (see section 16 for details of testing):

- 3 Month Toxicity Study in Rats, Final Report, July 4, 1984. GU project no. 820112, Ciba Geigy Limited, Basel, Switzerland.
- 90-day sub-acute oral toxicity study in albino rats, Final Report, 19 December 1973. IBT No. 622-03561, Industrial BIO-TEST laboratories, Inc., Illinois.
- 90-Day sub-acute oral toxicity study in Beagle dogs, IBT No. 651-03562, December 1973. Industrial BIO-TEST laboratories, Inc., Illinois.

Reproductive organs were analysed in the 90-day repeat dose studies with rats and dogs cited above. Treatment-related adverse effects on reproductive organs were not observed in these studies. The details of reproductive organs from these studies are summarized on pages 55-57.

Overall Conclusion: In all three 90-day subchronic studies there were no apparent effects on reproductive organs from the test material.

1. Study No. 820112 [1984]

In this 3-month oral toxicity study in rats, reproductive organs were examined grossly and microscopically. In the following table, reproductive organ weights and ratios are presented.

Table 1

Mean Organ Weight and Ratios

Male Rats

ORGANS	DOSE IN PPM									
	0.0		60.0		200.0		600.0		2000.0	
	NO.	MEAN	NO.	MEAN	NO.	MEAN	NO.	MEAN	NO.	MEAN
Body	20	469.079	20	466.364	19	475.399	20	480.414	20	485.079
Brain	20	2.444	20	2.462	20	2.448	20	2.415	20	2.449
Brain / Body	20	0.529	20	0.533	19	0.518	20	0.507	20	0.510
Gonads	20	3.649	20	4.005	20	4.041*	20	4.048*	20	4.146*
Gonads / Body	20	0.784	20	0.868	19	0.853	20	0.850	20	0.863
Gonads / Brain	20	149.165	20	163.055	20	165.401*	20	168.018*	20	169.600*

Female Rats

ORGANS	DOSE IN PPM									
	0.0		60.0		200.0		600.0		2000.0	
	NO.	MEAN	NO.	MEAN	NO.	MEAN	NO.	MEAN	NO.	MEAN
Body	20	288.155	20	290.864	20	287.904	20	290.679	18	281.688
Brain	20	2.267	20	2.263	20	2.303	20	2.283	19	2.252
Brain / Body	20	0.792	20	0.785	19	0.804	20	0.792	18	0.805
Gonads	20	0.183	20	0.169	20	0.162	20	0.201	19	0.182
Gonads / Body	20	0.064	20	0.059	20	0.057	20	0.070	18	0.065
Gonads / Brain	20	8.099	20	7.520	20	7.084	20	8.836	19	8.124

NO. = NO. OF VALUES/GROUP
* = SIGN. DIFFERENCE at 0.05

Statistical analysis of both absolute organ weights and organ to bodyweight ratios did not reveal any treatment-related effects. The increase in testis weights correlated with an increase in body weights and was not considered a treatment effect.

Gross necropsy and histopathological examination showed that reproductive organs were comparable among all treatment groups. Testes, epididymis, uterus, and ovary were examined.

2. Study No. 622-03561 [1973]

In a 90-day subchronic toxicity study in rats, all surviving rats following 90 days of feeding were sacrificed and autopsied. At the time of gross examination a complete set of organs and organ tissues were removed from each rat and examined.

Microscopic examination of testes, seminal vesicle, ovary, and uterus were carried out both in control and the 30,000 ppm groups.

Organ weight and ratio data of gonads is given below.

Table 2

Organ weight and ratio data (mean values)

Organ: Gonads

Dose (ppm)	Organ Weight		Organ/ Body Weight Ratio (g/100 g)		Organ/ Brain Weight Ratio (g/ g)	
	Males	Females	Males	Females	Males	Females
0	3.261	0.077	0.6338	0.0272	1.5121	0.0395
1000	3.325	0.084	0.6550	0.0301	1.5259	0.0417
3000	3.420	0.086	0.6438	0.0304	1.5965	0.0427
10000	3.393	0.076	0.6689	0.0280	1.5596	0.0389

No significant differences were noted between test and control rats for organ weights, gross effects or histopathological changes.

3. Study No. 651-03562 [1973]

In a 90-day subchronic toxicity study in beagle dogs, at dietary levels of 10000, 20000, and 30000 ppm, reproductive organs were examined for gross and histopathological effects.

Organ weight and ratio data of gonads is given below.

Table 3

Organ weight and ratio data
Organ: Gonads

Dose (ppm)	Organ Weight (g)		Organ/ Body Weight Ratio (g/1000 g)	
	Males	Females	Males	Females
0	16.8	0.907	1.69	0.086
	23.0	0.781	2.23	0.078
	18.9	0.779	1.45	0.092
	18.2	0.773	1.54	0.090
10000	11.6	0.753	1.12	0.084
	25.7	0.961	1.76	0.092
	13.4	1.004	1.25	0.100
	22.4	1.077	1.52	0.095
20000	15.7	0.456	1.38	0.059
	13.0	0.644	1.29	0.076
	20.1	0.830	1.69	0.078
	18.3	1.003	1.45	0.086
30000	20.4	0.756	1.85	0.072
	11.2	0.451	1.10	0.047
	13.1	0.154	1.39	0.013
	20.5	0.861	1.52	0.084

The weights of testes and ovaries were not significantly different among the treatment groups. Gross and histopathological examination of testes, ovaries and uterus did not show significant differences between control and test groups.